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THE PHYSIOLOGY OF MECHANICAL TRAUMA

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ANNUAL PROGRESS REPORT

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The Physiology of Mechanical Trauma

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ABSTRACT

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This report covers several areas of investigation in mechanical trauma. These are

1. The effect of operative trauma upon renal function following minor abdominal operations. Renal plasma flow and filtration rate appeared to increase slightly but significantly after lesser abdominal operations. Following large abdominal operations these functions are significantly depressed. Thoracic operations even of great magnitude do not depress renal function presuming that shock has not intervened.

2. Renal tubular necrosis and death in dogs during hemorrhagic shock: Relation to method of blood handling. Morbidity and mortality in dogs subjected to hemorrhagic shock is diminished by the use of heparin and is also diminished by the omission of all wetable surfaces from the exsanguination and retransfusion system.

3. Oxygen consumption during shock in dogs. Methods for measuring oxygen consumption during shock are described and the usefulness of the measurement of this parameter is indicated.

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ARMY PROGRESS REPORT

SECTION I

THE EFFECT OF OPERATIVE TRAUMA UPON RENAL FUNCTION

During the 1940's the marked effect of hemorrhagic and traumatic shock upon the kidneys was amply demonstrated both experimentally and clinically in the classic studies of Lauson et al, Phillips et al, and Bywaters. These observations led investigators to question the effect operative trauma had upon renal function as contrasted to the effect of shock. Ariel in 1950, Habif et al in 1951, and DeWardener in 1953 and 1955 reported on the effect of anesthesia and operation on renal function. All of these investigators agreed that anesthesia per se had a profound depressing effect on renal blood flow and on glomerular filtration rate; however, operation itself seemed to add no further depression to these parameters and following the end of operation and anesthesia, renal function returned promptly to normal levels within ten to fifteen minutes. These studies included patients undergoing a wide range of procedures from hernia repair to subtotal gastrectomy.

Following the unanimous reports of these investigators, little attention was given in the following years to the question of operative effects upon renal function. Clinicians continued to note, however, that an occasional patient following a major operation without apparent complications (no evidence of transfusion reaction, no evidence of prolonged shock at operation, and no evidence of pre-operative renal damage) developed acute renal failure post-operatively. This was most commonly observed in patients following resections of abdominal aneurysms. The predilection of the patient with abdominal aneurysm resection to suffer renal failure was pointed out by Doolan et al, and by Powers. Powers suggested that this was a reflex phenomenon due to the cross clamping of the aorta and could be prevented by blocking the nerves of the renal pedicle. Gangon et al, Aukland, McGonigle et al, and Berry et al have been unable to demonstrate this reflex in dogs or in humans.

Recently, Kragcland (1960) and Gullick and Raisz (1961) have reported that there is some depression of renal function following major operations which is not attributable to the direct effect of anesthesia. Krageland found a 50% depression of the creatinine clearance in more than half of the patients he studied and Gullick and Raisz noted that the patients' ability to raise urine osmolarity was impaired following the operation in many instances. This work has led us to further evaluate the problem of post-operative renal function.

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MATERIALS AND METHODS

PAH and Inulin clearances were determined the day before operation and five hours after operation in a group of 43 patients. Patients 50 years of age and older were selected as being a group which would be most likely to show post-operative renal change. Pre-operative renal function was normal as determined by urinalysis, serum urea nitrogen, and clinical history. The types of operations studied were classed as large abdominal operations, including subtotal gastrectomy and hemicolectomy; moderate abdominal operations, including exploratory laparotomy and biopsy, chdlecystectomy, vagotomy and pyloroplasty; thoracic operations, including lobectomies and pneumonectomies; and abdominal aneurysm resections.

The renal clearance tests were done according to the constant infusion technique of Smith, Goldring and Chasis as modified by Shock. Infusion of fluids was regulated with a tunnel clamp. All clearances were studied for a minimum of three periods. During pre-operative periods in which urine flow was high, period lengths of ten minutes were sometimes used. Post-operatively all periods were at least fifteen minutes in length and sometimes a half hour. Because of the recurrent question as to the effect of osmotics on renal flow, no osmotic diuretics were used to promote renal flow either pre or post-operatively. A multieyed straight catheter was used for bladder drainage in male patients and a mushroom-tipped catheter was used for bladder drainage in female patients. Analytical methods previously described were used (Shock 1946).

The pre-operative renal function levels in these patients diminished with age as noted by Davies and Shock, and Lowenstein et al. The slope of regression in age in these 2 studies and the present one were very close.

RESULTS

Individual results in all patients together with their mean and standard deviations are recorded in the first table. Of the patients in the first group undergoing minor intra-abdominal operations there were 8 patients ranging in age from 56 to 84. Glomerular filtration rate rose at 5 hours after operation in every patient. Renal plasma flow also increased in some patients, but this change was not as great or as consistent as the rise in glomerular filtration rate. The filtration fraction also increased in 6 of the 8 patients chiefly due to the rise in the glomerular filtration rate.

The 5 patients undergoing operations on the chest ranged in age from 53 to 70. They required in every instance blood transfusions to maintain them during operation. Despite this the results in this group were not far different

from those in the first group. Glomerular filtration rate rose somewhat and a moderate increase in renal plasma flow was also seen although it was not found in all patients. Again filtration fraction was increased.

Those patients undergoing extensive intra-abdominal operations showed a definite and significant fall in both renal plasma flow and in glomerular filtration rate. Filtration rate fell somewhat less than renal plasma flow resulting again in increase in the filtration fraction.

Finally, in those patients operated on for abdominal aneuryams, both renal plasma flow and glomerular filtration rate decreased after observation with a rise in the filtration fraction largely due to a greater fall in plasma flow than in glomerular filtration rate. These changes were not markedly different than those found in patients undergoing other major intra-abdominal operations. Statistical analysis of the data was done and indicated the levels of significance noted in Table 2.

DISCUSSION

These results indicate an increase in glomerular filtration rate and renal plasma flow after lesser abdominal operations. These changes are significant and have not been previously reported. The reason that these changes were not previously observed may be that many of the early workers followed their patients through operation with repeated clearance determinations and for an hour or two after operation. When renal functions return to normal at a point one or two hours post-operatively observations of renal functions were discontinued. If functions had been studied over a longer period the changes reported here would presumably have been apparent. The cause for this increase is not entirely clear. The increase in glomerular filtration rate may be explained as a result of constriction of the efferent glomerular vessels. The rise in renal plasma flow might be related to the transient increase in cardiac output which has been reported to follow less extensive operations.

The patients who underwent thoracic operations showed no significant difference from those patients undergoing minor intra-abdominal procedures. All of these patients required blood transfusions in the course of their operations often amounting to as much as 2 or 3 units compared to the previous group, none of whom had required blood transfusions. It appears that transfusions per se do not play a role in renal functional changes after operation. The observation that thoracic operations do not depress renal functional changes in these older patients is of special interest considering the observations of Ladd in surveying renal functional changes in Korean casualties. He found that patients following chest wounds were much less likely to have renal functional depression and that post-operative renal failure was much less common in this group of patients.

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Of the 15 patients undergoing larger abdominal operations there was a significant depression post-operatively in glomerular filtration rate and renal plasma flow. These findings suggest that the postoperative depression in renal functions may be affected both by the site and by the magnitude of the operation. Such factors as the disturbance of the ureters in the course of reflecting the peritoneum during colon resection and abdominal perineal resection and the pressure of packs on the kidney and ureters in the course of both upper and lower abdominal operations may play a role in this. Again it is puzzling why post-operative depressions following these larger operations have not been noted. Review of most of the previous studies suggest however that not enough patients were studied to divide the operations according to site as well as to magnitude. Moreover, the age groups studied were not as homogenous as in the current study.

Finally, in those patients undergoing aneurysm resection depression in renal function also occurred. However, the magnitude of these depressions was no greater than that noted in other patients undergoing other larger abdominal operations and the difference between these two groups is not statistically significant. Beall has reported that renal functions in this group of patients are depressed as long as 24 to 48 hours post-operatively when the normal pre-operative regimen of water deprivation after midnight is followed. His studies indicate that this drop in renal function may be related simply to dehydration. In any case, it would appear that cross clamping of the aorta is not the decisive cause for this decrease in renal function since similar depressions are noted following similar abdominal operations in which cross lapping of the aorta is not done.

Decreases in glomerular filtration rate and in renal plasma flow can produce alterations in the sodium reabsorption in the renal tubules. Therefore, it appears that post-operative changes in renal function, at least in the first few hours after operation may account for some of the changes noted in post-operative electrolyte excretion.

Since all of those studies here reported were conducted in patients 50 years of age and over, conclusions must be confined to this age group. The findings suggest that it would be worthwhile to conduct similar studies in younger patients. Serial studies during the entire 24 or 48 hours post-operative would be most useful.

SUMMARY

Studies of glomerular filtration rate, renal plasma flow, filtration fraction in 29 patients after various types of operations indicate that the site of operation and the magnitude of operation affect these renal functions in patients of this age group. Lesser abdominal operations and chest operations are followed by a modest but significant elevation of glomerular filtration rate and plasma flow. Larger abdominal operations are associated with a significant drop

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in both renal plasma flow and glomerular filtration rate again with a rise in filtration fraction. The depression of renal function following abdominal aneurysm resection does not appear to differ from that seen in other abdominal operations of similar magnitude

Number	AGE Year	SURFACE AREA Sq.M.	PRE-OPERATION Inulin Clearance cc/min/1.73 Sq.M.	PRE-OPERATION PAH Clearance cc/min/1.73 Sq.M.	PRE-OPERATION Filtration Fraction %	POST-OPERATION Inulin Clearance cc/min/1.73 Sq.M.	POST-OPERATION PAH Clearance cc/min/1.73 Sq.M.	POST-OPERATION Filtration Fraction %
				MINOR INTRA-ABDOMINAL OPERATION				
5	65	1.50	116	485	23.9	129	606	21.2
17	84	1.60	72	306	23.5	104	268	39.1
21	68	1.68	96	378	25.4	124	367	33.5
24	56	1.73	98	435	22.5	130	379	34.3
33	72	1.73	96	466	20.6	124	466	26.6
40	73	1.50	63	296	21.3	71	309	22.9
41	[illegible]	1.55	45	150	23.3	65	188	30.4
43	70	1.73	105	366	28.7	119	472	25.2
M		1.62	86.4	360.3	23.7	108.1	381.9	27.9
Std/Dev		0.10	23.93	109.5	2.53	24.87	134.2	6.36
				CHEST OPERATION				
2	53	1.73	104	646	15.8	111	502	22.0
9	70	1.40	77	327	23.6	82	370	22.0
[illegible]	[illegible]	1.30	133	626	21.0	149	548	27.3
[illegible]	56	1.90	121	648	18.6	190	754	25.2
34	62	1.73	78	401	19.4	49	466	10.5
M		1.61	102.6	496.8	19.7	116.2	521.1	21.4
Std/Dev		0.49	25.16	151.9	2.56	55.30	142.3	6.33
				ABDOMINAL ANEURYSMS				
20	67	1.73	96	546	17.6	--	440	--
23	68	1.82	69	340	20.1	15	53	28.6
28	63	2.00	84	253	33.2	35	165	21.1
32	53	2.05	124	[illegible]	23.3	134	552	24.2
M		1.85	89.6	427.0	22.1	61.3	302.5	24.3
Std/Dev		0.16	21.8	127.2	6.05	63.72	232.21	3.79

	AGE	SURFACE AREA	PRE-OPERATION			POST-OPERATION		
			Inulin Clearance cc/min/1.73 Sq.M.	PAH Clearance cc/min/1.73 Sq.M.	Filtration Fraction %	Inulin Clearance cc/min/1.73 Sq.M.	PAH Clearance cc/min/1.73 Sq.M.	Filtration Fraction %
Number	Year	Sq.M.						
EXTENSIVE INTRA-ABDOMINAL OPERATIONS								
5	82	1.68	74	263	28.1	52	131	39.7
7	63	1.60	88	297	29.6	66	275	24.0
10	76	1.52	79	382	20.6	52	167	31.3
12	54	1.10	89	327	27.2	16	59	26.3
13	51	1.73	141	788	17.8	159	713	22.0
14	72	1.70	88	342	25.7	86	228	37.7
15	72	1.40	84	412	20.4	85	367	23.2
16	68	1.73	94	517	18.4	94	352	26.7
18	69	1.45	81	320	25.3	100	384	26.1
19	55	1.60	63	230	27.5	79	314	25.0
22	64	1.48	114	663	16.9	79	293	27.0
35	79	1.77	109	438	24.9	41	247	16.6
36	88	1.48	41	346	11.7	26	314	8.1
31	74	1.73	86	451	19.0	61	363	16.8
30	77	1.73	122	509	24.0	164	663	24.8
M		1.58	85.2	419.6	22.4	77.34	324.7	25.4
Std/Dev		0.18	24.8	170.5	5.09	41.84	149.3	7.86

STATISTICAL ANALYSIS

Lesser abdominal operations compared with other operated groups

	GFR	RPF	FF
Thoracic Operations	0.5	0.4	0.8
Larger Abdominal Op.	<0.01	<0.01	0.2
Aneurysm Resections	<0.01	<0.01	<0.01
Aneurysms compared with Larger Abdominal Op.	0.20	0.7	0.4

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SECTION II

THE PRODUCTION OF RENAL TUBULAR NECROSIS IN DOGS BY HEMORRHAGIC SHOCK AND THE EFFECT OF BLOOD HANDLING

Sometime ago while engaged in some experiments on hemorrhagic shock, we noted that after long periods of moderate shock small infarct-like lesions were found in the renal tissue of dogs. The extent and number of these lesions were found to be related in some degree to the amount of heparin that the animals were given in the course of the experiments. On examining the literature it was found that these findings duplicated and confirmed the findings of Hardaway et al who had reported that the heparinized dog was more resistant to hemorrhagic shock than the nonheparinized animal and who had noted similar renal lesions as well as lesions elsewhere in his animals following varying periods of shock. During subsequent personal communication with Johnson and Hardaway, Johnson noted that the method in which blood was handled seemed to affect the extent and number of renal lesions found and that these lesions seemed to be related at least partly to the amount of wetable substances in the blood handling system such as glass and steel three-way stopcocks. On the basis of this observation we embarked on a project of evaluating the effect of both heparin and of non-wetable systems on the response of hemorrhagic shock in dogs.

METHOD

A total of 156 mongrel dogs were used. The dogs were restrained on an animal operating table. Under local anesthesia a cutdown was made over the femoral artery and vein. The femoral artery was cannulated with a polyethylene cannula. When a wetable system was used this cannula was connected by way of the polyethylene tubing to a regulation hospital three-way stopcock and then by way of further plastic tubing to a glass bottle. In the nonwetable system the polyethylene tubing was connected directly to a plastic tubing leading to a plastic blood transfusion bag. Blood was removed from the dogs by allowing them to bleed into the receptacles at a given level so that they acted as "Lamson bottles." The level of shock selected in all animals was moderate and a mean pressure of 90 mm. of mercury was maintained. Blood was returned to the animals at the end of the shock period in the wetable system by means of a glass syringe attached to the three-way stopcock. In the nonwetable system blood was returned to the animal by means of a pressure cuff around the plastic blood transfusion bag. A cutdown was also done on the contralateral groin and a catheter placed in the femoral artery on this side. This catheter was used to measure blood pressure in the animals by connecting it with a mercury manometer

and it was also used for the collection of arterial blood samples. The animals were divided into five experimental groups. In the first group (A) the animals were given a total of a minimum of 100 mg. of heparin and were bled into a wetabl system. Dogs in this group were subjected to periods of 2, 4 and 6 hours of shock. In Group B the same experimental setup was used except that the amount of heparin given was reduced 50 mg. Periods of shock evaluated were 2, 4, 6 and 8 hours. Animals in Group C used the same experimental setup as in the previous two groups, but no heparin at all was used. Blood in the reservoir and in the tubing was kept liquid with the use of a standard ACD solution. These dogs were subjected to periods of shock of 1 or 2 hours. Longer periods resulted in 100 per cent mortality and therefore attempts at evaluating shock in animals of this group beyond the period of two hours were abandoned. Dogs in Group D were given no heparin and in addition a plastic nonwetable reservoir system was used in removing and replacing blood. Periods of shock of 2, 3 and 4 hours were evaluated. Dogs in Group E were not subjected to shock, but were treated by removing 50 cc of blood in a glass syringe from one femoral artery and simultaneously replacing it with 50 cc of blood from another dog in the contralateral femoral artery so that over the period of 2 hours of shock a good deal more blood was exposed to nonwetable surfaces than in the previous experiments, but the dogs were never in shock over this period.

RESULTS

The results are indicated in the table. It is apparent that in those animals treated with heparin and a wetable system that the mortality rate was relatively low and that even after 6 hours of hemorrhagic shock only 2 of 9 of these animals died. Reducing the amount of heparin by half, however, markedly increased the mortality rate of the animals and in animals exposed to 6 hours of moderate shock the mortality rate was 47 per cent. Renal tissues taken from those animals who survived 2 to 4 days following these experiments showed renal tubular necrosis in 89 per cent of those animals subjected to 6 hours of shock. Group C indicates the dramatic difference produced by removing all heparin from the system when dogs were permitted to hemorrhage into and to receive blood back from a wetable system. After only one hour of shock, 20 per cent of the dogs died and 70 per cent of the survivors showed obvious renal lesions. After 2 hours of shock using this system, 5 of 6, or 83 per cent, of the animals expired and in the one surviving animal massive tubular necrosis occurred. Group D on the other hand shows the response which follows hemorrhaging an animal into a totally wetable system. Here there were no deaths in any of the dogs after 2, 3 or 4 hours of shock. Examination of the renal tissues still showed occasional small areas of renal necrosis. However, the number of areas and the extent of the lesions was much reduced and they wer found much more rarely than in the dogs of Group C.

Finally, experiments described in Group E were performed to determine what the effect of blood handling alone was in these experiments. None of these animals were in shock and none of them died, although one of the five animals

did show a small area of renal necrosis. This was quite tiny. The renal tubular lesions found in these experiments were scattered areas of cortical ischemic necrosis, in some instances involving almost the entire cortex. Comparing them with findings in humans, they resembled more closely the lesions of renal cortical necrosis rather than the lesions described in post-traumatic renal insufficiency. They also closely resembled the lesions found in dogs treated with epinephrine instilled into the renal artery such as reported by Hatcher et al. Other tissues were also examined in these dogs and areas of ischemic necrosis were also found in the liver and in the small bowel. The heart, lungs and brain were never found to be involved. The lesions appeared most commonly in the kidneys, second most commonly in the liver and were found least often in the small bowel.

CONCLUSIONS

Death and renal tubular necrosis during experimental hemorrhagic shock in dogs is markedly affected by the use of heparin. Heparin in large enough amounts will almost abolish both mortality and renal lesions during long periods of moderate shock. If no heparin is used the mortality in such experiments will be high after relatively short periods of shock if a wetable system is used. If a nonwetable system of handling blood is substituted, mortality is abolished and although renal tubular lesions occasionally occur they are minor in comparison. In preparing standardized models of hemorrhagic shock in dogs strict attention must be paid to the type of anticoagulation used, the amount used, the presence or absence of wetable materials in the tubing and reservoir systems and the gentleness with which the blood is handled.

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SECTION III

OXYGEN CONSUMPTION DURING SHOCK IN DOGS

In the final analysis shock in man and animal is the result of failure to properly maintain metabolism at the level of the cell. Many of the parameters which are measured in order to measure shock are at best indirect indications of this failure. One of the most direct parameters which can be measured is the consumption of oxygen by the animal during the period of stress. Maintenance of adequate oxygen consumption indicates adequate delivery of oxygen to cell and utilization in the cell. A diminishing oxygen consumption indicates failure of delivery of oxygen to the cellular units and/or failure of these units to utilize oxygen. As shock deepens both factors are probably implicated. Guyton and Farish in 1959 devised an oxygen consumption recorder which they have used successfully in measuring many of the variations in oxygen consumption during the shock period. We feel that such an apparatus has considerable research and clinical application and thus have currently developed a device for monotoring oxygen consumption and are applying it to a number of research problems in shock.

MATERIALS AND METHODS

A standard spirometer was modified by replacing the tubing with standard anesthesia gas tubing and couplings. The output end of the spirometer was connected to the intake part of a standard Harvard variable rate and volume piston respirator. Gas from the cylinder of the respirator was fed into the dog's tracheo-bronchial tree by way of a cuffed tracheal tube and the return flow from the dog was fed back into the tank of the spirometer through anesthesia tubing. By fixing the stroke rate and volume of the respirator at any level above the normal oxygen consumption of the experimental animal and by filling the tank of the spirometer with oxygen, the oxygen consumption of the animal could be monitored continuously over long periods of time. Alterations in consumption could be noted with each stroke of the respirometer so that total response delay of the system was based on the stroke rate. A number of preliminary experiments have been performed using this device. During these experiments and venous and arterial oxygen in the experimental animals were measured at intervals with the use of a Wilson-Jay gas chromotography unit. Knowing both venous and arterial oxygen levels plus total oxygen consumption allowed cardiac output to be calculated on the basis of the effect principle as previously noted by Guyton. Serum sodium, potassium, CO_2, chloride, pH and osmolarity were also measured periodically in our animals.

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In preliminary experiments oxygen consumption has been measured in 5 untreated control animals, in 7 animals following spleenectomy, and in 12 animals in varying stages of shock.

RESULTS

These preliminary findings indicate that the described mechanism for measuring oxygen consumption is reliable and reproducible. The finding of others that shock diminishes oxygen consumption in relation to the degree of blood loss is confirmed. It is noted that an oxygen debt is accumulated during the period of shock and that the ability of the experimental animal to recover from shock appears roughly correlated with his ability to restore his oxygen debt following retransfusion.

DISCUSSION

These initial experiments have encouraged us to feel that this method is a usable one for monetary shock and the methods of modification of shock in the experimental animal and in other clinical circumstances. It is anticipated that the effectiveness of vasopressors, vasoconstrictors, anticoagulants and various degrees of acidosis and alkylosis can be more effectively explored with the use of this additional tool.

Section III

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